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ACUTE NEPHRITIS IN CHILDREN, WITH SPECIAL REFERENCE TO THE TREATMENT OF UREMIA[1]

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Ever since the epoch-making discovery of Richard Bright, students of nephritis have been endeavoring to devise a classification[2] for this disease which would be acceptable to physiologist, pathologist and clinician. That they have failed is not surprising when the many difficulties surrounding nephritis are taken into consideration. In the adult, the etiology and pathology are often clouded by the variety of chemical and bacterial agents which, acting persistently and repeatedly, may affect the renal structures in different ways, and by the element of time which permits of the development of a multiplicity of anatomical changes. The symptoms presented may likewise be obscured by unrelated cardio-vascular changes and strains resulting from the "wear and tear" in the adult organism. But because in childhood such confusing conditions are seldom found, it may be said that the young child, who never has been ill previously, affords an unusual opportunity for studying certain aspects of nephritis.

Nephritis in children differs from nephritis in adults in that the acute are far more common in children than the chronic forms. Chronic nephritis, it will be recalled, is the form chiefly seen in adult clinics. In children the forms of this disease most frequently encountered are acute glomerular nephritis and acute tubular nephritis. There are, however, a small number of cases which present symptoms common to both these forms. The frequency of nephritis in children is illustrated by the series of 46 cases which form the basis of this

[1] Read before the Academy of Medicine, Toronto, Ontario, Feb. 18, 1926. Received for publication, May 20, 1926.

[2] The simple division of nephritis, into acute and chronic forms, has been adopted quite generally by clinicians as it furnishes a conservative, yet useful, working basis.

report.[3] There were only 5 cases of chronic nephritis. In 41 cases of acute nephritis the acute glomerular form occurred in 24 and the acute tubular form in 14 cases. There were 3 cases of the mixed form. Nephritis as it occurs in children differs still further from nephritis in adults in that in the majority of the acute cases it is possible to postulate, with a considerable degree of accuracy, the character of the underlying pathologic process when the history of onset and the distinguishing clinical symptoms are correlated with the laboratory findings. This is especially true in differentiating the acute glomerular from the acute tubular variety.

As is generally known, the kidneys in the glomerular form are somewhat enlarged, and the glomeruli stand out distinctly as fine red points. Practically all of the glomeruli are more or less involved. The tubules, being an essential part of the renal unit, show changes which in all probability are secondary to, and to a large extent dependent upon, the glomerular injury. The degree of fibrosis or scarring is directly proportional to the severity and duration of the process. In the other type of nephritis—acute tubular—notable changes in the kidneys are their large size, the loss of normal striations and the presence of edema and pallor. Degenerative lesions are the characterizing feature. The proximal and distal convoluted tubules are the seat of diffuse lipoid formation and there is very little evidence of cellular response. The glomeruli are but slightly, if at all, involved, even when the process has entered the subacute stage. Slight fibrosis with sparse lymphocytic infiltration may be found, however, in places. From this brief description it can be seen that the predominating lesions in acute glomerular nephritis are in the glomeruli. Degenerative changes involving the uriniferous tubules are distinctive of acute tubular nephritis. In this latter form the term nephrosis, as proposed by Müller, Volhard and Fahr, is quite generally used in contradistinction to nephritis, inasmuch as the histologic changes are degenerative rather than proliferative in nature. It is reasonable to suppose that in the mixed form of nephritis the kidneys show lesions representative of both types.

This report deals with the prominent clinical and laboratory features of these two forms of kidney disease in children and with the cause and treatment of uremia complicating acute glomerular nephritis.

[3] Patients suffering from scarlet fever, diphtheria and mineral poisoning have not been included in this series.

The onset in each form is distinctive and characteristic. Often the history in acute glomerular nephritis is as follows: The patient is taken acutely ill with malaise, anorexia, fever and sore throat. After being ill for several days he improves so as to be "up and about the house," or he recovers so completely as to return to his former activities. Later, after an interval of several days, the mother notices that the urine is "bloody," or the school teacher observes "puffiness" about the eyes. Less frequently the onset is more stormy. The patient, following an interval of apparent recovery from an acute infection, complains of headache and visual disturbances: these symptoms continue with vomiting, and suddenly convulsions supervene. Hematuria, while always present, may not have been noted previously. Quite the reverse picture characterizes the onset of acute tubular nephritis. Invariably it is insidious and seldom is there a history of an acute infection antedating the illness. A child who had been regarded previously as normal and in good health is observed to have a "puffy" appearance about the eyes or to have swelling of the ankles. The edema gradually increases until a large part of the subcutaneous tissues becomes involved extensively and to a high degree. Some patients even with marked edema are "up and about," playful and do not appear ill, others are fretful and irritable, or they may even be quiet and drowsy; often they are exceedingly uncomfortable, especially when the edema is extreme. During intervals, if free from edema, they exhibit no particular subjective or objective symptoms, save possibly a secondary anemia. Alarming symptoms such as visual disturbances and convulsions are seldom observed. Fever is not present constantly but periodic febrile reactions frequently occur.

The urine in these two forms of nephritis is suggestive of the nature of the underlying changes in the kidneys. In the acute glomerular form the urine has a distinctive "smoky" color due to the presence of blood. Red blood cells may persist for days, even after the gross evidences of blood have disappeared. In the acute tubular form the urine is clear with high specific gravity (1025–45) and *albumin* is the significant finding, frequently amounting to from one to three grams per liter. The sediment in acute glomerular nephritis contains all forms of casts, many erythrocytes and leucocytes, while the sediment in acute tubular nephritis contains hyaline, granular and waxy casts,

leucocytes and doubly refractive lipoid substances. The *absence of erythrocytes* in the latter condition is notable. The following observations apply equally well to both forms; the volume is diminished only slightly in some patients, but in others it may be decreased to the point of complete anuria; the excretion of phenolsulphonephthalein may be normal or diminished during the acute stages (25 to 40 per cent in two hours); later, as the renal injury lessens, normal amounts are excreted. Cultures from the urine are invariably sterile.

Although accumulation in the blood of nitrogenous products is frequently found in acute glomerular nephritis, it is important to bear in mind that the severity of the general symptoms is not necessarily dependent on the amounts of nitrogenous products retained or on the volume of urine excreted. Thus in one patient with anuria who died, the urea N was 28 mg., whereas in another fatal case without anuria the urea N was 115 mg. per 100 cc. of blood. Analysis of the blood in the patients with acute tubular nephritis reveals normal or only slightly increased amounts of non-protein nitrogen, which is in striking contrast to the increased retention of nitrogenous products which may be found in the former type. A low plasma protein in which the globulin fraction exceeds the albumin fraction is a constant and significant finding in acute tubular nephritis. The value for total protein may be less than half that of the normal. In glomerular nephritis, the plasma protein is normal.

Gamble and Hamilton, as well as other investigators, have found that changes in various ionic factors in the plasma are not constant in either form of nephritis. Low or high values for plasma chloride and low and normal values for plasma bicarbonate may be obtained. Hamilton, in our laboratory, has found also that in tubular nephritis the total fixed base of the plasma is quite regularly reduced, while in the acute glomerular form it remains within normal limits. Acidosis has been by no means a constant finding in either form. In a few of the patients it was due to an increased concentration of the chloride ion and not to a retention of phosphate as has usually been assumed to be the cause of acidosis in nephritis (Marriott, Howland, Denis, and Minot).

Edema in acute glomerular nephritis, although present, may be so slight as to be appreciable only by frequent weighings. In acute

tubular nephritis generalized edema is the notable and distinguishing symptom. Beginning usually in the face, the edema may increase rapidly and spread to the entire subcutaneous tissues, so that with the eyelids tightly closed, the genitalia distended and the entire body enormously swollen, the patient becomes a picture of abject misery. Free fluid rapidly accumulates in the thoracic, pericardial and peritoneal cavities. Marked variation in the degree of edema and in its location may be seen from day to day, and may occur without evident cause. On the other hand, the edema may be influenced by recurrent or intercurrent infections or by therapeutic measures. In the patients with acute tubular nephritis studied by us there has been manifested a close relationship between edema, urinary output and albuminuria. When the edema was at its height, there was diminution of urine and the amount of albumin was excessive. With less or no visible edema, the water intake and output balanced properly and the amount of albumin often was negligible. We have never observed edema without albuminuria and cylindruria.

An interesting observation relating to the type of edema may be noted in these two forms of nephritis. In the majority of cases of acute glomerular nephritis, edema is seldom characterized by "pitting" and the tissues reflect a feeling of tenseness quite unlike the soft "pitting" edema in the tubular form. In both forms the weight of the brain is increased when compared with the normal and on section there is an increased fluid content. The brain in acute glomerular nephritis is firm and tense and the convolutions are flattened, whereas in acute tubular nephritis the brain is soft and spongy but the convolutions are normal in appearance. Whether these variations in the type of edema are due to a difference in the location of the retained water in the tissues (intracellular or extracellular), and whether they are of pathologic significance, remains to be determined.

Various theories to explain the cause of edema in nephritis have been advanced, but up to the present time the pathogenesis remains shrouded in mystery. It seems quite evident that the edema in acute tubular nephritis cannot be explained altogether as a consequence of defective renal function. As regards this point the more important causes, outside the renal structures, which have been considered are: osmotic pressure changes, changes in the affinity of the tissue colloids

for water and changes in the permeability of the capillary walls. Prominent among the factors which influence water transfusion are the proteins of the body fluids. The patients in this series confirm the fact, already pointed out, that plasma protein is constantly lower than normal in acute tubular nephritis. It is possible that this lowering may be explained in part by the loss in the urine of large amounts of protein, particularly albumin. In any case, this change tends toward a disturbance of osmotic relationship between the blood and tissue fluids. This relationship would be still further disturbed by an increased permeability of the capillaries to protein, which would cause a higher concentration of protein in the tissues. The recent work of Claussen is of much significance in this connection. He has found that the surface tension of the serum is lowered and that a substance which changes the permeability of membranes for proteins is present in the blood and urine of patients with tubular nephritis. As the edema disappears, the surface tension returns to normal and the substance which affects the permeability of membranes disappears from the urine and blood. Confirmation of Claussen's findings may lead us nearer to an understanding of the causation of edema in this form of nephritis.

The observations in this series of cases also confirm the already established facts regarding the arterial tension in these forms of nephritis. In acute glomerular nephritis, the blood pressure was usually increased and in the severe cases there appeared to be a relationship between the degree of edema and the height of the arterial tension. In acute tubular nephritis the arterial tension was normal or only slightly increased and it was not dependent on the degree of edema. We shall refer later to the relationship between edema and arterial tension in acute glomerular nephritis.

It is generally accepted that the severity of acute glomerular nephritis is gauged by the degree of edema, the amount and persistence of hematuria, and by oliguria and anuria. But although all of these signs are of value, we believe that in children with this form of nephritis a *steadily rising blood pressure* and the development of cerebral symptoms are most important danger signals. The observations made in this series of cases show that little apprehension need be felt concerning edema, hematuria, or even a scant urinary output, so long as the systolic

blood pressure remains around 110 to 130 mm., but on the other hand, with a steadily rising blood pressure and with vomiting, headache, and visual disturbances, appropriate therapeutic measures should be instituted. Frequently we have seen patients with no visible edema, small amounts of blood in the urine and voiding relatively large amounts of urine, exhibit alarming symptoms as the blood pressure rose. It should be kept in mind that a patient may develop an increase in blood pressure with grave symptoms at any stage of the disease.

Complete recovery from the acute glomerular form takes place in a majority of cases. In our series of 24 patients, twenty-one recovered and three died, uremia being the cause of death in the latter. There are no criteria, connected either with the gravity of the symptoms or with the duration of the disease, from which one can tell in which cases complete healing may be expected. That chronic nephritis only rarely follows acute glomerular nephritis has been shown by Ernberg, Dorch, James and others. They have re-examined many adults who had suffered from nephritis before fifteen years of age and only about ten per cent showed evidences of persistence of the disease.

Acute tubular nephritis tends to run a subacute or chronic course, in so far as evidenced by periodic remissions and exacerbations; nevertheless, recovery is frequently seen even after the symptoms have persisted over a period of many months. We recall two patients with recurring attacks of edema and albuminuria lasting for many months, both of whom have been in perfect health for 6 and 10 years, respectively. The prognosis, however, is less favorable than in the glomerular variety of nephritis. Secondary infection is usually the cause of death in tubular nephritis. Five patients in this series died: one of streptococcus septicemia, four of streptococcus peritonitis. Two patients have developed chronic nephritis, five have apparently recovered, and two are unimproved.

We wish next to indicate certain points concerning the rôle which bacterial infection may play as one of the causative factors in these two forms of nephritis.[4]

[4] We shall not attempt to consider at this time whether nephritis is a general systemic disease with the renal changes merely an incident in the course of the disease, or whether the general symptoms are secondary to the structural changes in the kidneys.

Many writers have called attention to the frequency with which acute diseases due to the hemolytic streptococcus precede the onset of acute glomerular nephritis. In our series of cases, tonsillitis in 14, otitis media in 3, acute respiratory infections in 2, and laryngitis in 1 case preceded the onset of renal symptoms. A hemolytic streptococcus was recovered from the rhinopharynx in 14 of the 24 patients. Throat cultures were not made in the remaining 10 patients. Inasmuch as the hemolytic streptococcus is found in a large percentage of cases of acute glomerular nephritis, it seems justifiable to conclude that the injurious effects, in all probability, are brought about through the agency of a toxin elaborated by this organism. This assumption by analogy is not unreasonable in view of the discovery of the toxin of the hemolytic streptococcus of scarlet fever and because of the many points in common between acute glomerular nephritis and the nephritis complicating scarlet fever.

In acute tubular nephritis the association of an acute disease and the demonstration of a specific organism are less constant. The onset of symptoms suggesting nephritis in this series of cases was preceded by tonsillitis in 1 patient, and by an acute respiratory infection in one patient. There was no history of a recent acute infection in the remaining 12 cases. The failure to determine a primary infection preceding the appearance of albuminuria and generalized edema in this form of nephritis is all the more remarkable when contrasted with the frequency with which acute glomerular nephritis follows an acute infection. As was noted, out of 24 patients with acute glomerular nephritis, 20 gave a definite history of a primary infection, while a definite history of an antecedent illness was present in only 2 of the 14 patients with acute tubular nephritis.

Claussen and Marriott believe that the staphylococcus is the infecting organism which most frequently causes acute tubular nephritis. Marriott refers to 20 cases in which they found the primary source of infection in the paranasal sinuses, with the staphylococcus as the infecting organism. Munk, on the other hand, found in his cases that among the bacteria which may cause the disease the pneumococcus was the most common organism. In our patients observed with this point in mind we have been unable to determine the presence of any infecting organism or even to localize a primary focus of infection.

Five patients in this series were under almost continuous observations from the onset of the disease until its termination by death. In not one of these could a primary focus of infection be demonstrated, either by roentgenograms or by direct cultures from the rhinopharynx and accessory sinuses. Hemolytic streptococci were cultivated from the blood at the time of death in one patient. Four other patients died of a generalized peritonitis due to the hemolytic streptococcus. It is appreciated fully that patients with this form of nephritis are peculiarly susceptible to intercurrent infections with various types of organisms and that the demonstration of a hemolytic streptococcus at the end is not proof that it was the primary causative factor. It is known that diphtheria toxin and the toxin of scarlet fever produce renal symptoms and general symptoms which cannot be distinguished during certain stages by clinical or laboratory means from the form of nephritis under discussion. While bacterial infection is the probable cause of acute tubular nephritis, it is felt that sufficient evidence has not yet been accumulated to single out as the chief offender any particular microörganism.

Summarizing the distinguishing features in these forms of nephritis, it is seen that increased arterial tension and the development of the group of cerebral symptoms described as uremic are characteristic events in acute glomerular nephritis, whereas generalized edema without rise in blood pressure is the outstanding feature in acute tubular nephritis. In acute glomerular nephritis red blood cells are the conspicuous finding in the urine; the plasma protein is normal and the non-protein nitrogen tends to increase in the blood. In acute tubular nephritis large amounts of albumin and lipoid substances are found in the urine; the plasma protein is low and the non-protein nitrogen in the blood is normal. The distinguishing features in these two forms are shown in Table I.

Now, as regards uremia in children with acute glomerular nephritis, we wish to present certain observations which have resulted from a study of 11 patients with this complication.[5] These patients were suffering from acute nephritis following tonsillitis or acute respiratory infections. In addition to the cerebral symptoms (vomiting, head-

[5] The drawings and charts are reproduced through the courtesy of the Boston Medical and Surgical Journal.

ache, visual disturbances, coma or delirium and convulsions), there was hypertension,[6] hematuria, and visible though not necessarily marked edema. The patients were treated during the uremia, or as we prefer to say, the "cerebral symptoms" of this form of nephritis, with intravenous injections of a one per cent solution of magnesium sulphate and by the administration of large amounts of magnesium sulphate by mouth and by rectum.

The following case history is cited to illustrate the course of the disease and the effect of the treatment used (Chart 1).

TABLE I

Distinctive features of acute nephritis in children

FEATURES	ACUTE GLOMERULAR	ACUTE TUBULAR
Onset	Acute	Insidious
Urine	Blood	Albumin
N.P.N.	Increased	Normal
Serum protein	Normal	Low
Edema	Slight	Marked
Arterial tension	Increased	Normal
Uremia	Frequent	Rare
Recurrence	Rare	Common
Fatal termination	Uremia	Secondary infection
History of infection	Common	Rare

The patient (R. K. aged 6 years) was admitted to the hospital with acute glomerular nephritis ten days after an attack of acute tonsillitis. The physical examination was negative except for a moderate degree of generalized edema. The urine was "smoky" in color, and there was albumin with many red and white cells and granular casts. The non-protein nitrogen was 30 mg. per 100 cc. of blood. The urinary output in the first 24 hours was 780 cc. and the fluid intake was 1200 cc. The phenolphthalein test was 45 per cent in 2 hours.

Course and treatment. On admission the patient weighed 38 pounds. The systolic blood pressure was 120 mm. During the next few days there was a steady increase in weight and a gradual increase in blood pressure. The patient vomited frequently and seemed most uncomfortable from headache. When the blood pressure reached 160 mm. systolic the patient weighed 39½ pounds, a gain of 1½ pounds in 6 days. He complained of difficulty in seeing and suddenly became irrational and had a convulsion. 150 cc. of a one per cent solution of magnesium

[6] Both systolic and diastolic values were raised.

sulphate were then injected intravenously, and as the systolic blood pressure fell to 115 mm., the cerebral symptoms promptly subsided. A second injection was given after five hours as the blood pressure had risen to 145 mm. systolic. Catharsis was induced by large doses of magnesium sulphate by mouth. Three days later, with the blood pressure remaining at a low point (110 mm.) it was found that he weighed 36½ pounds; a loss in weight of 3 pounds.

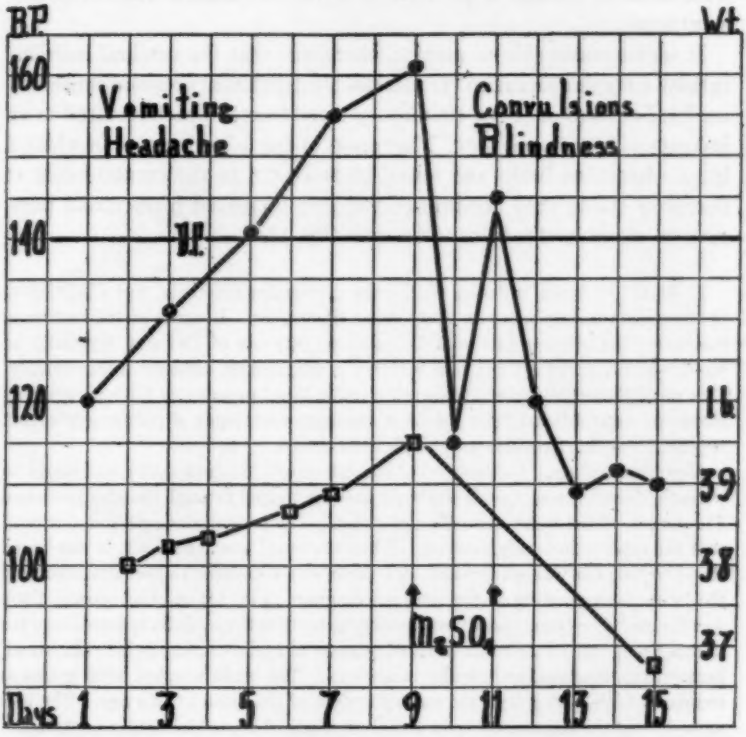

CHART 1. ACUTE GLOMERULAR NEPHRITIS WITH CEREBRAL SYMPTOMS—TREATED BY INTRAVENOUS INJECTION OF $MgSO_4$ SOLUTION

Similar observations made on each of the eleven patients studied show clearly the relationship which exists between (1) the cerebral manifestations, (2) the blood pressure and (3) the edema in this form of uremia. As the blood pressure rose, the patients vomited, became irritable and complained of headache. Edema and continued rise

in blood pressure, visual disturbances, coma and convulsions followed almost invariably. Decrease of edema and lowering of the blood pressure were coincident with the disappearance of cerebral symptoms. The symptoms were not dependent upon the amounts of non-protein nitrogen in the blood or the degree of hematuria and anuria, as they were no more marked in patients with than in patients without uremic symptoms.

It seems reasonable to assume, therefore, that the cerebral manifestations were due either to (1) increased intracranial pressure caused by cerebral edema, or (2) to circulatory disturbances which resulted in an increase of blood pressure. The report of the following case in which a huge edematous brain was found incarcerated in the cranial vault at necropsy shows that cerebral edema and increased intracranial pressure do occur in this form of uremia (Fig. 1).

E. McG., 6¼ years, suffering with acute glomerular nephritis, was admitted to the hospital ten days after an acute rhinopharyngitis. Because of the vomiting, headache, disturbances in vision and a blood pressure of 150 mm. (systolic) he was given 150 cc. of a 1 per cent solution of magnesium sulphate intravenously. This was followed by improvement and a fall in blood pressure to 130 mm. systolic. However, several hours later the blood pressure rose, signs of pulmonary edema appeared and shortly afterwards respiration ceased.

Necropsy findings. On removal of the calvarium the dura mater was found so tense that when it was opened the brain literally bulged through the small incision. The surface of the brain was pale and moist. The convolutions were so flattened that the sulci were barely evident. When the brain was taken out, it was found that the medulla was compressed and there was a circular impression involving the base, corresponding to the foramen magnum (Fig. 1); in other words, there was the medullary cone phase so commonly seen when the medulla is forced into the foramen magnum as the result of rapid increase of brain volume, as in brain tumor, hemorrhage, fracture, and similar conditions. The brain weighed 1500 grams as compared with 1200 grams, the normal weight of the brain at this age. The kidneys showed the anatomical lesions characteristic of acute glomerular nephritis.

Further proof of the increase in intracranial pressure in this form of uremia may be demonstrated by lumbar puncture which yields an increased amount of cerebrospinal fluid under greatly increased pressure. In our experience this may be present *early* in the course of uremia, while *later* in the course, or in the terminal stage, the cerebrospinal fluid may not be increased in amount nor the tension raised.

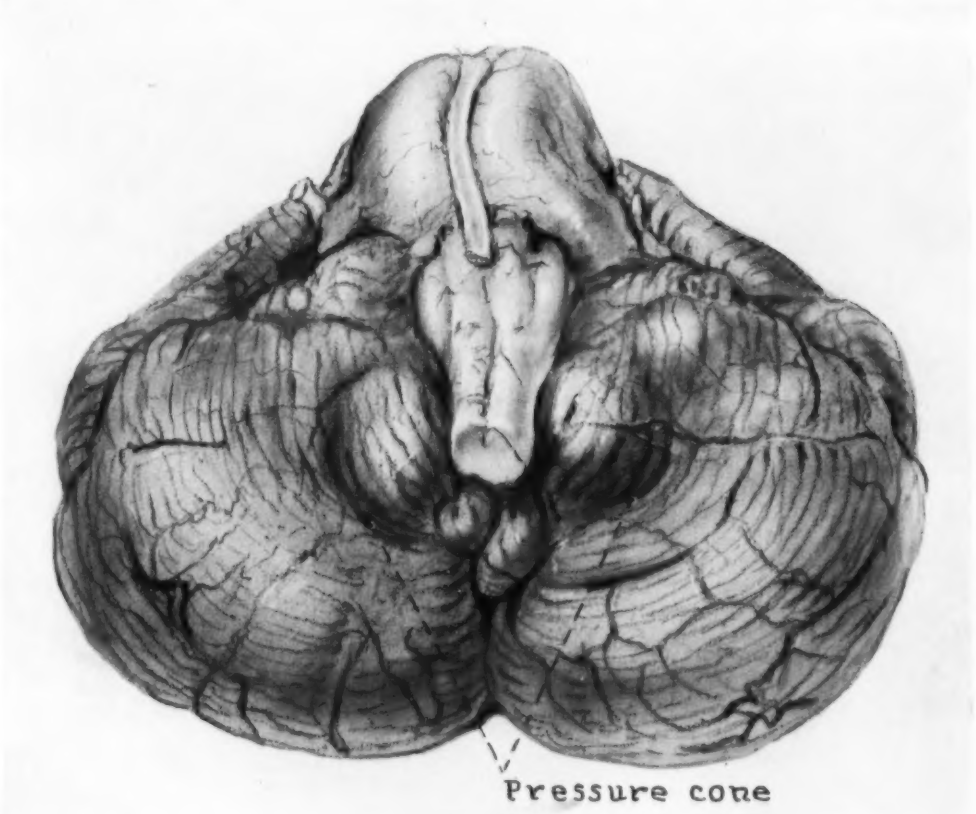

FIG. 1. MEDULLARY CONE PHASE, COMPRESSION OF MEDULLARY STRUCTURES, FLATTENED CONVOLUTIONS, INDISTINCT SULCI

This variability in the degree of intracranial tension, as judged by lumbar puncture, has been used as an argument against intracranial tension playing an important rôle in the production of uremic symptoms. This argument seems untenable, however, when the factors that determine the free interchange of cerebrospinal fluid between the cerebral and the spinal subarachnoid systems are recalled. The foramina between these systems could easily be compressed by an edematous brain so as to prevent any evidence of increase in tension in the spinal subarachnoid space or even small amounts of cerebrospinal fluid being obtained by lumbar puncture. The observation of cerebral edema and increased intracranial pressure in this form of uremia is not new. It has been mentioned by Noeggerath, Volhard, M. Fischer and others.

Concerning arterial hypertension in uremia, Volhard and Fahr mention that rising blood pressure precedes or is closely associated with the development of the cerebral symptoms. These writers conclude that it has not been proved whether the symptoms, together with the increased blood pressure, result from circulatory disturbances in the brain, or whether the symptoms are secondary to the arterial hypertension. Marriott believes that hypertension in acute glomerular nephritis is due to general capillary constriction and that the uremia is due not to renal insufficiency but to a toxin, possibly the same as the one which causes the capillary damage. Foster and others have suggested that a toxic base extractable from the blood of uremic patients causes the symptoms. Kylin, who has studied the capillaries, refers the arterial hypertension in acute glomerular nephritis to a capillary hypertension. Boas, on the other hand, found no evidences of glomerular nephritis in four patients with high capillary pressures and in a number of his cases of glomerular nephritis he found the capillary pressure normal. It has been shown by Cushing that when compression of the brain was produced in dogs, the arterial pressure rose as the intracranial pressure was increased and that fatal symptoms occurred when the intracranial pressure approximated or exceeded the arterial tension. This experiment demonstrates clearly that increased arterial tension may be the result of increased intracranial pressure and that the rising blood pressure may be looked upon as a compensatory adjustment. In the patients reported in this series, increased arterial

tension paralleled the degree of edema and the cerebral symptoms followed with regularity the increase in blood pressure. It was found also that, as the edema became less, the arterial tension fell and that it remained at a low level after the edema had disappeared. It is not to be denied that alterations in the capillaries may be the primary cause of the edema. However, careful consideration of the clinical symptoms and the pathological anatomical findings suggest strongly that the cerebral symptoms may readily be explained on the basis of cerebral edema and increased intracranial tension and that the arterial hypertension is, partly at least, the result of the edema of the brain.

The therapeutic results afford additional proof that increased intracranial pressure is the primary cause of the uremic symptoms. Early in the investigation an hypertonic solution of sodium chloride and sodium carbonate, as recommended by M. Fischer, was used in treating a patient with uremia (Chart 2). This boy (A. B., 6½ years) was brought to the hospital with acute glomerular nephritis following an acute tonsillitis. Before the intravenous injection the patient was having generalized convulsions and the blood pressure was 155 mm. systolic and 110 diastolic. As the solution was injected, the convulsions ceased and the blood pressure fell to 130 systolic and 90 mm. diastolic. As long as the systolic blood pressure remained about 130 mm., the general condition of the patient was much improved. Several days later, as the blood pressure began to rise, the patient vomited and complained of headache; convulsions occurred when the arterial pressure reached 160 mm. systolic. It was then found that 200 cc. of a one per cent solution of magnesium sulphate injected intravenously had the same beneficial effect as the hypertonic solution of sodium chloride and sodium carbonate—the convulsions ceased, the blood pressure fell to 120 mm. and the patient lapsed into a quiet sleep. Although he was much improved, a second injection of magnesium sulphate was given the next day, as the blood pressure was rising. The blood pressure returned to normal and remained so after this injection and the patient was discharged at the end of fifty-one days apparently well. It should be noted that the first injection was an hypertonic solution of sodium chloride and sodium carbonate. As it has been shown by Weed, McKibben, and others that intravenous injection of hypertonic solutions reduce brain volume, the result

of the hypertonic injection in this case is further evidence favoring the assumption that the cerebral symptoms were due to increased brain volume and increased intracranial tension. The second injection was a one per cent solution of magnesium sulphate. Although this is an

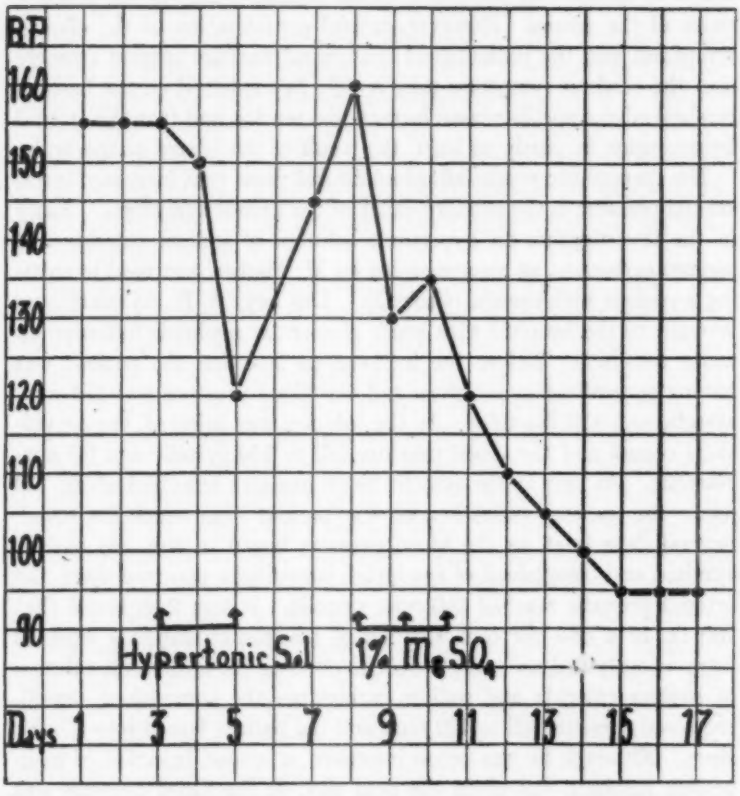

CHART 2. EFFECT OF HYPERTONIC AND HYPOTONIC SOLUTIONS ON ARTERIAL TENSION

hypotonic solution (Hall and Harkins), the result of this injection was, clinically, exactly the same as when the hypertonic solution was given. The mechanism of its action will be discussed later.

Further evidence favoring the conception that the increased intra-

cranial pressure which results from edema is the cause of the cerebral symptoms and that the high blood pressure is secondary to it is found in observing the development of generalized edema, and the arterial tension when the treatment is directed against the edema alone. This point is well illustrated in the following case.

A. T., aged 8 years, was ill with sub-acute nephritis. As shown in Chart 3, the systolic and diastolic blood pressure rose steadily as the edema increased. (The degree of edema was determined by frequent weighing.) As the blood pressure rose, the patient vomited and complained of severe headache. When the blood pressure reached 180 mm. systolic and 120 mm. diastolic and the patient had gained 16 pounds in weight, large doses of magnesium sulphate were given by mouth. In the following two weeks the edema disappeared and the blood pressure fell correspondingly. The patient lost 16 pounds and the blood pressure fell from 180 mm. systolic to 110 mm. systolic.

It is most unlikely that magnesium sulphate would have so effectively relieved the arterial hypertension and edema by direct influence on the blood vessels or the neurogenic mechanism of the brain. In so far as is known, this salt acts as a diuretic (Gamble, Blackfan and Hamilton) and as a cathartic when administered by mouth.

The treatment of uremia occurring in the course of acute glomerular nephritis by intravenous injections of one per cent magnesium sulphate has, as stated before, given most favorable results. We have used this method in 11 cases; in 8 cases the patients recovered promptly from their alarming symptoms, but 3 patients who were in the terminal stage died. This form of therapy, although most effective in relieving cerebral symptoms and arterial hypertension, should not be resorted to unless there are such presenting symptoms as visual disturbances, delirium, convulsions, and arterial hypertension. When the solution is injected slowly at the rate of 2 cc. per minute there is not observed any change in respirations or in the pulse rate; if, however, it is injected rapidly, irregular respirations with a fall in the pulse rate may occur. In one case the blood pressure fell thirty points after 25 cc. (0.025 gm. $MgSO_4$) of the solution had been given within 2 minutes. This we think was probably due to a sudden release of intracranial pressure following too rapid introduction of the solution. Urinary retention or evidences of renal irritation have not followed the use of this solution. The immediate effect of such an injection on the blood pressure

is shown in Chart 4. It should be remembered that the action of this solution intravenously is to effect a prompt fall in blood pressure with rapid relief of the cerebral symptoms. The course of the disease,

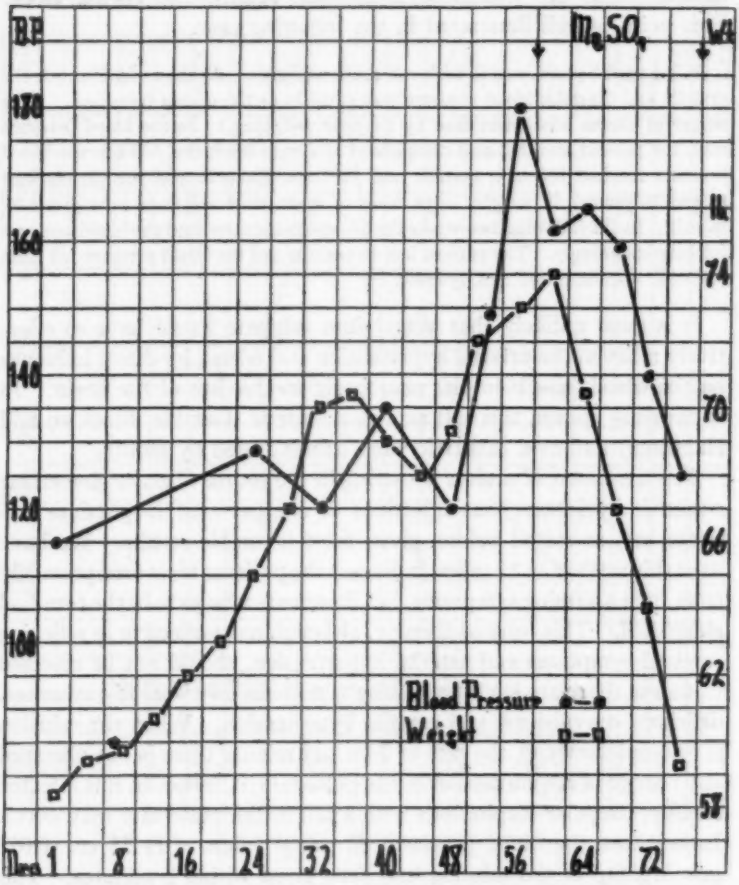

CHART 3. EFFECT OF $MgSO_4$ (ORAL) ON EDEMA AND BLOOD PRESSURE

as evidenced by the renal symptoms, however, is not altered. The fall in blood pressure during the procedure is the best index as to the total amount to use. Frequently diaphoresis and diuresis follow,

but when injected intravenously magnesium sulphate does not exert a cathartic effect. The duration of the effect is from five to twelve hours so that a rise in blood pressure with return of the alarming symptoms may be expected unless active measures directed against

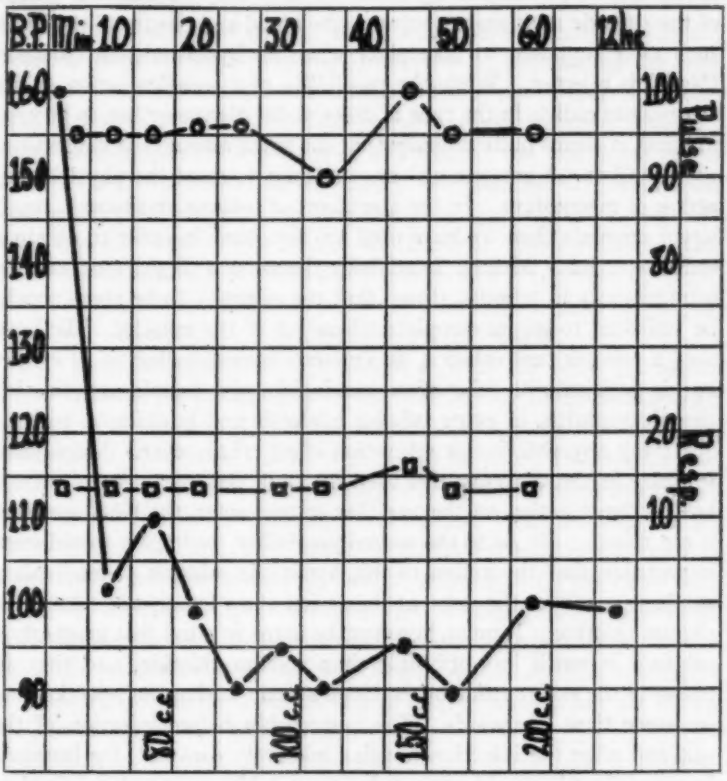

CHART 4. IMMEDIATE EFFECT OF $MgSO_4$ (INTRAVENOUS) ON BLOOD PRESSURE, PULSE, AND RESPIRATION

the generalized edema are instituted. This is best accomplished by the administration of magnesium sulphate by mouth and by rectum. It has been our custom to use 1 to 1½ oz. of a 50 per cent solution of magnesium sulphate by mouth every four or six hours, and 2 to

3 oz. of the same solution by rectum every six hours. Excessive dehydration should be avoided.

In explanation of the action of a one per cent solution of magnesium sulphate two possibilities are presented: (1) The action may be due to the sedative effect of magnesium or (2) it may be due to a change of the osmotic relationship between the blood and tissues of the brain such as is supposed to take place when an hypertonic salt solution (NaCl) is injected. While the possibility of a sedative action of the magnesium radicle in the type of cases under discussion has to be kept in mind, it seems quite unlikely that the small amounts of magnesium used (0.05 to 0.1 gm. per kg.) are sufficient to exert the physiological action of magnesium. In the treatment of tetanus and tetany, much larger amounts than we have used are necessary in order to obtain a sedative action. Meltzer, in advising the use of a six per cent solution intravenously in tetanus, stated that the quantity to be given should be sufficient to secure complete relaxation of the muscles. We have used a one per cent solution (in amounts corresponding to 10 cc. per kg.) in patients with tuberculous meningitis, with uremia complicating chronic nephritis, in acute tubular nephritis and in animals, without observing any sedative or relaxation effect whatsoever. Magnesium sulphate in the concentration used by us in the treatment of uremia has no direct action on the vascular system when the blood pressure is not raised. (2) As to the second possibility, perhaps it would seem improbable that the action of this hypotonic solution of magnesium sulphate would be the same as the action of an hypertonic solution of sodium chloride. It must, however, be borne in mind that magnesium sulphate is much less diffusible than sodium chloride, and that an excess of the salt remains in the blood stream during the injection and for some time afterwards. The hemoglobin before injection of the salt and after the injection remains relatively constant; for instance, in one patient it was 74 per cent before and 73 per cent after injection. In one patient in whose case the total fixed base of the blood before and after the injection of magnesium sulphate was determined, it was found that after injection the total base was increased by 6 cc. N/10. These findings may therefore be interpreted as suggesting that the beneficial action may be due to an increase in the total concentration of electrolytes in the blood, which thus alters the osmotic

relationship between the blood and tissues. Further studies regarding the action of this solution are in progress.

If edema of the brain, as suggested by these observations, is an essential factor in this form of uremia, then the sequence of events which so consistently takes place can be rather clearly postulated. A rapid encroachment on the intracranial space from the increasing cerebral edema results in a steady increase of intracranial pressure, which in turn initiates the vomiting, headache, convulsions and other symptoms. The arterial tension[7] increases correspondingly, inasmuch as the regulatory mechanism is so adjusted by the vasomotor center that the arterial tension is always held in excess of the external pressure exerted by the compressing force (in this case edema) against the arterioles and capillary vessels in the medulla. Fatal bulbar anemia ensues, accompanied by pulmonary edema, and is followed by cessation of respirations, when the vasomotor center fails to keep the arterial tension in excess of the increased intracranial tension.

The observations herewith presented support the view that edema of the brain is the initial cause of the cerebral symptoms and arterial hypertension in acute glomerular nephritis in children. It should be emphasized that these studies were made in young children so that arterio-sclerosis, cardiac hypertrophy and advanced renal lesions can be excluded as factors requiring consideration. Explanations for the development of edema, or reasons for its involvement of the brain in one patient and not in another patient suffering with the same form of injury are purely speculative in view of our present knowledge.

In conclusion we wish to emphasize the following points:

1. The form of uremia seen in acute glomerular nephritis in children is usually preceded by a steady rise in arterial tension and by visible but not necessarily marked edema.

2. Intracranial tension resulting from edema of the brain is probably the causative factor of the symptoms in this form of uremia.

3. Arterial hypertension is probably the result of increased intracranial pressure.

[7] The cerebrum accommodates itself readily to slowly forming intracranial tension as in tumors, hydrocephalus, and to the accumulation of fluids as in meningitis, so that the arterial tension need not always be increased in these conditions.

4. The intravenous injection of one per cent solution of magnesium sulphate together with the administration of large doses of the salt by mouth and by rectum has been found to be effective in the treatment of this form of uremia.

5. Intravenous treatment is not effective during the medullary cone phase or in the terminal stages.

6. Lumbar puncture should be used guardedly in order to avoid incarceration of an edematous brain in the foramen magnum.

7. It is suggested that the characteristic symptoms with arterial hypertension be referred to as the cerebral symptoms of acute glomerular nephritis.

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LACTIC ACID IN THE TOXEMIAS OF PREGNANCY

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Eclampsia is associated with a pronounced increase in the lactic acid content of the blood, as was noted by us in a recent publication (1). It was this finding which made it imperative for us to ascertain whether similar changes could be demonstrated in the other types of pregnancy toxemia. With this in mind, we have studied the blood lactic acid in certain cases of nephritic toxemia and low reserve kidney. It should be noted that in grouping the toxemic cases in this Clinic, we follow the classification recently outlined by Stander and Peckham (2). All our lactic acid determinations were made on blood specimens taken before breakfast from patients resting in bed. Throughout our study we employed the method of Clausen (3), using the procedure of Meissner and Schneyer for the formation of acetaldehyde from lactic acid, in which 50 per cent sulphuric acid is allowed to react at 140°C. with the filtrate to be analyzed. It must be emphasized that this method is not specific for lactic acid, but may apply to other α-hydroxy-acids. In all our analyses the Folin-Wu blood filtrates were made within an hour after the blood had been drawn from the arm vein of the patient, and the sugar was immediately precipitated with 10 per cent $CuSO_4$ and 5 per cent suspension of $Ca(OH)_2$. The procedures employed for the determination of the other blood constituents mentioned in this paper are those referred to in our previous publication.

In normal pregnancy, we find that the lactic acid content of the blood is practically identical with that observed in normal non-pregnant women. For the former, we reported variations between 12 and 32 mg.; while for normal non-pregnant women the average was 29 mg. per 100 cc. of blood.

[1] Fellow of the C. R. B. Educational Foundation.

TABLE I

Low reserve kidney

CASE NUMBER	DATE	N.P.N.	SUGAR	CO_2	URIC ACID	LACTIC ACID	ALBUMIN	PHTHALEIN	REMARKS
								per cent	
1	3– 3–26	35.7	118	47.5	2.8	75.7	0.5	60	Admitted 9 months pregnant, with oedema of legs and B.P. 150/94.
	3–22–26	44.4	83	51.9	3.5	15.7	0		Pressure falls gradually and oedema disappears. Delivered of normal child. Discharged in good condition and with normal B.P.
2	1–26–26	33.3	81	48.3		36.2	1.0	72	Mild toxemia with slight headache and oedema. B.P. 150/100. At term
	2– 3–26	31.2	107	49.9		16.9	0.5		Patient better. No complaint. No headache, no oedema. Discharged in good condition at end of puerperium
3	On admission	32.4	74	46.3		73.8	0.5	52.5	No symptoms. Rising B.P. for past 2 months. Near term. Labor induced, in view of B.P. 194/124. Discharged in good condition
4	On admission	25.5	81	43.9		51.6	0.6	60	Eclampsia in 1910. 15 abortions. Slight oedema of ankles. B.P. 138/92. This pregnancy again ended in abortion at 5½ months
5	On admission	28.0	87	45.3	4.1	44.4	0.5	54	Oedema of legs and headache for past 3 months. At term. B.P. 180/100. Labor induced. Live child. Discharged in good condition with normal B.P.

TABLE I—*Continued*

CASE NUMBER	DATE	N.P.N.	SUGAR	CO_2	URIC ACID	LACTIC ACID	ALBUMEN	PHTHALEIN	REMARKS
								per cent	
6	On admission	27.7	95	46.4	4.1	38.6	Trace		Slight oedema. B.P. 160/116. Labor induced on day of admission. Discharged in excellent condition with normal blood pressure
7	On admission	27.1	110	38.4	2.7	30.2	Trace		Some headache. No oedema. B.P. 156/98. Discharged in good condition B.P. 132/78
8	On admission	23.0	70	50.2		19.8	3.0	60	Headache for 1 week. Oedema of legs for past 10 days. B.P. 160/110. Discharged at end of puerperium in good condition with B.P. 114/60 and no albumin in urine

LOW RESERVE KIDNEY

The findings reported in Table I for pregnancy complicated by low reserve kidneys indicate a definite increase in lactic acid in the blood, as well as a relationship between such elevation and the severity of the morbid process. Moreover, where more than one determination has been made, the values show a fall in lactic acid as the patient improves. In general it may be stated that a lactic acid content of over 40 mg. per 100 cc. of blood may be regarded as definitely above the upper limit of normal. Table I shows several borderline cases in which the lactic acid varies between 30 and 40 mg., but in four others it is decidedly increased, reaching 75.7 mg. in Case 1. The values for the other blood constituents reported are within the limits for pregnancy with low reserve kidney.

TABLE II

Nephritis complicating pregnancy

CASE NUMBER	DATE	N.P.N.	SUGAR	CO_2	URIC ACID	LACTIC ACID	ALBUMIN	PHTHALEIN	REMARKS
								per cent	
9	2- 2-26	55.4		30.5	8.0	104.3	5.5		Admitted 1-28-26 with B.P. 204/110. Oedema for past 2 weeks. Heart enlarged
	2- 4-26	33.7	95	40.2	8.9	43.3	1.2	33	Improved. Oedema disappeared. Delivered of hydatidiform mole
	2-10-26	26.1	105	47.9		23.3	Trace	53	In good condition. Discharged 2 days later
10	1-26-26	40.0	75	44.5		53.9	8.0	65	Primipara—2 months from term. Headache and marked oedema for past 3 weeks B.P. 170/110
	2-23-26	24.0	123	46.2		40.2	1.0		Improved. B.P. 150/100. Premature, spontaneous delivery on 2-5-26. Discharged later in good condition
11	2-25-26	54.6	111	46.2		52.5	3.0	55	Oedema of legs. Headache. B.P. 184/120. At term
	2-29-26	25.6	60	52.2		42.6	++		Patient improved. B.P. 110/75
12	1-27-26	30.3	61.5	43.4		76.2	1.0	70	Pregnancy toxemia in 1925. Trace of albumin and rising B.P. for past month. At term. B.P. 155/100. During 2nd stage of labor patient had 1 convulsion. No more convulsions. Improved rapidly and discharged in good condition. Probably a very mild case of eclampsia, instead of nephritis complicating pregnancy

NEPHRITIS COMPLICATING PREGNANCY

In Table II we give the findings in three cases of definite nephritis and in one with a mild eclampsia. In all four patients, there is a lactic acid content well above the normal. In the nephritic cases we were able to obtain two sets of analyses on each, and in each of them improvement of the patient is accompanied by a decrease in the non-protein nitrogen, the blood lactic acid and the albumin in the urine, as well as by a rise in the CO_2 combining power of the blood. In the severe cases the phenolsulphonephthalein kidney test shows a decreased output of dye, which increases as the patient improves.

DISCUSSION

I. Accumulation of lactic acid associated with renal impairment

We have seen that pregnancy complicated by low reserve kidney or by nephritis is accompanied by an increase in the amount of lactic acid in the blood, and it appears to us that this may be the result of one of several factors or of a combination of two or more of these factors. In the nephritic group there is renal impairment sufficient to produce retention of non-protein nitrogen, as well as a delayed excretion of phenolsulphonephthalein. That such renal impairment might be associated with a lowered excretion of lactic acid, should be considered. As the patient improves, the return of the lactic acid to a normal level is accompanied by a disappearance of the nitrogenous retention, a decrease or disappearance of the albumin in the urine and a fall in blood pressure. In how far certain types of renal involvment may be accompanied by an accumulation of lactic acid is certainly a problem worthy of further investigation; but it does not seem probable to us that impaired kidneys, as such, play any significant rôle in its retention, for the reason that most, if not all, of the lactic acid is normally reconverted into glycogen.

II. Increased formation of lactic acid

It is well known that lactic acid may arise from carbohydrate or from the carbohydrate fraction of the protein molecule. In the normal person it is formed during muscular contraction, which consists of two

phases, and it is during the first, or contractile, phase that some form of carbohydrate is converted into lactic acid; while part or all of it is resynthesized to glycogen during the second, or recovery, phase during which oxidation occurs. There seems to be no reason to suppose that in the two types of toxemia of pregnancy under discussion, the accumulation of lactic acid may result from increased muscular contraction. On the other hand, lactic acid may come from the decomposition of protein (4), and furthermore, the possibility that it may arise from fat (5) must not be overlooked. Unfortunately, our information concerning this type of lactic acid production is too scanty to allow any further discussion.

III. Disturbance in the resynthesis of lactic acid into glycogen

As has already been pointed out, it is in the recovery phase of muscular contraction that lactic acid is reconverted into glycogen. This is an endothermic reaction and the energy for it must be supplied from the outside. There is some evidence that this is effected by the oxidation of part of the lactic acid (6, 7). On the other hand, it seems probable that in certain conditions the energy required for the reconversion of lactic acid into glycogen comes from other sources.

It is conceivable that a disturbance in the oxidative processes of the body may seriously interfere with the reconversion of lactic acid into glycogen and so result in an accumulation of lactic acid. It seems quite clear that removal of lactic acid is accomplished by oxidation, by synthesis into glycogen or "lactacidogen" (8), and by the formation of sodium lactate, which is carried to other tissues, such as the liver or muscles, where it may undergo chemical changes. Clausen (9) sums up the question by saying: "Whenever the circulation or the processes of oxidation become insufficient, the rate of removal of lactic acid will be less than the rate of its production, so that the lactic acid concentration in the blood will rise and the alkali reserve of the tissues (including the blood plasma) will fall."

IV. The relation between CO_2 and lactic acid

Anrep and Cannan (10) found that the lactic acid concentration of the blood rises and falls with the pH of the blood. They concluded

that the hydrogen-ion concentration of the blood regulates the removal of lactic acid. Barr, Himwick and Green (11), on the other hand, indicated in their studies on muscular contraction that lactic acid accumulation is the chief cause of the reduction in CO_2 capacity. In the work of Clausen (9) and others (12, 13), we have additional evidence of the existence of a type of acidosis due to lactic acid, or definitely associated with an increased amount of it in the blood-stream.

It is not clear whether the acidosis associated with certain cases of severe toxemia of pregnancy is due to an accumulation of lactic acid or whether it has a retarding effect on the removal of lactic acid. Our investigations along these lines are not sufficiently advanced to permit us to make any definite statement.

CONCLUSIONS

1. In pregnancy complicated with low reserve kidney, the lactic acid in the blood is increased. This accumulation of lactic acid disappears as the patient improves.

2. In pregnancy complicated with nephritis, there is a similar accumulation of lactic acid in the blood, which disappears with the improvement of the patient.

3. The factors which may possibly play a rôle in the accumulation of lactic acid in these two types of pregnancy toxemia are:

a. Decreased elimination of lactic acid.

b. Decreased oxidation and interference with the resynthesis of lactic acid into glycogen.

c. A possible disturbance of the hydrogen-ion concentration of the blood.

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THE INFLUENCE OF CHANGES IN THE HYDROGEN ION CONCENTRATION UPON THE REFRACTORY PERIOD OF THE PERFUSED MAMMALIAN HEART[1]

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In an earlier paper from this laboratory (1) it was shown that it is possible to control accurately the rate of beating of the perfused dog's heart by an alteration in the pH of the perfusion fluid alone between so limited a range as 7.0 and 7.8, the cardiac rate being accelerated on the alkaline side and slowed on the acid side of normal pH 7.4. Coincidently with the change in rate following upon a change in the pH of the perfusate it was also demonstrated that there occurred an alteration in the P-R interval paralleling in a measure the change in rate, an increase in the hydrogen-ion concentration of the perfusate being always associated with a lengthened A-V and a decrease with a shortened A-V conduction time.

Upon the basis of these results it was suggested that the rhythm and rate of conduction were controlled, in large measure, by the pH of the fluid bathing the cardiac tissue.

The observations detailed in this study were carried out with the purpose of determining whether or not under given constant conditions of cardiac rate, with a variation only in the hydrogen-ion concentration of the perfusion fluid, any definite relationship could be shown to exist between the refractory period in the perfused mammalian heart and the pH of the perfusion fluid.

EXPERIMENTAL

The dog's heart was used exclusively in the experiments outlined below: It was isolated, perfused and removed from the thorax by the method previously described (1). Standard Locke's solution, thoroughly oxygenated and heated to 37°C. by means of glass coils pass-

[1] Received for publication June 12, 1926.

ing through an electrically controlled water-bath, was used as the perfusate. By the use of a three-way tap it was possible to shift abruptly from a perfusate of normal pH 7.4 to 7.0 or 7.8 as desired. With the exception of a few instances the observations were carried out and completed within a period of from 20 to 60 minutes. It was felt that observations recorded after a longer time interval represented too artificial conditions, and that changes might occur as a result of the prolonged perfusion which could not be entirely dependent upon the experimental conditions. It is of interest in this connection that in those instances in which the experiment was carried on over a longer period the actual results obtained, as shown by our measurements, maintained essentially the same relationship seen in the shorter experiments, the reaction of the cardiac tissue as a whole being simply slowed up, and the very distinct differences under a varying pH coming out clearly. In determining the refractory period, the method employed was essentially that described by Lewis (5). Two galvanometers were used. The string of one, having suitable resistance interposed, records the rhythmic break shocks and the interrupting break shock, while the string of the second records the electrogram from direct leads attached to the heart.

In order to avoid the confusion arising from the variation in rate following a change in the pH of the perfusate and to standardise the criteria of the experiment, the heart was driven at a constant rate, a Lewis rotary contact maker being employed. The refractory period was determined by means of a timing device designed on the principle of the automobile sparking timer as described elsewhere (3). The ratio of the interrupting to the driving stimulus was as 1 to 6, the interrupting stimuli being carried to the heart through the driving contacts. In analysing our curves no measurements of the interrupting break shock were made unless they were preceded by at least two effective rhythmic driving shocks. It is well known that the refractory period is modified by the preceding pause; hence the necessity for this precaution.[2] The stimulating electrodes and the two

[2] In our timing device, as at first designed, the ratio of the interrupting to the driving stimulus was as 1 to 3. We found, however, that this was too close a relationship, and that satisfactory curves could only be obtained by using a 1 to 6 ratio, and our interrupter was accordingly so modified.

pairs of recording electrodes were placed in line at intervals varying from 10 to 12 mm. apart and attached respectively to either the auricular or ventricular muscle surface.

It is obvious that what we have determined as the refractory period represents the time interval from the occurrence of the signal, the deflection of the first string, to the onset of the response as evidenced by the deflection of the second string. We have not determined the refractory period from the exact point of stimulation and to this extent our results are open to the same criticism that is applicable to all recorded determinations of the refractory period in muscle. The galvanometer connections were made by means of worsted kaolin paste electrodes attached by threads directly to the heart. The recorded curves were measured by a Lucas comparator. In all, a series of 17 hearts were studied, from which we have selected as thoroughly satisfactory experimental observations the instances tabulated below. In each experiment the heart was driven at a rate sufficiently above that of the spontaneously beating auricle to ensure a constant control of the cardiac cycle under the conditions of the experiment. Following a change in the pH of the perfusion fluid an interval of from three to ten minutes was allowed for the heart to become adapted to the altered hydrogen-ion concentration.

TABLE I

Auricular muscle. Expt. 30. Auricle

TIME	pH	NUMBER OF RECORD	DRIVEN RATE	SECONDS AFTER SIGNAL		CALCULATED REFRACTORY PERIOD
				Latest ineffective response	Earliest effective response	
4.28	Changed to 7.8					
4.35	7.8	14	111	0.177	0.178	0.177
4.36	Changed to 7.0					
4.41	7.0	16	111	0.189	0.196	0.192
4.42	Changed to 7.8					
4.47	7.8	17	111	0.175	0.188	0.181

In determining our measurements the results were carried out to the fourth decimal place. The fourth figure has been dropped in these tables as unessential.

In Table I three determinations of the refractory period of the auricular muscle are recorded following earlier observations upon the ventricular muscle. The significant difference in the recorded

TABLE II

Expt. 34. Auricle

TIME	pH	NUMBER OF RECORD	DRIVEN RATE	SECONDS TO SIGNAL		CALCULATED REFRACTORY PERIOD
				Latest ineffective response	Earliest effective response	
3.16	Changed to 7.0					
3.21	7.0	2	100	0.172	0.174	0.173
3.28	Changed to 7.8					
3.31	7.8	5	100	0.148	0.160	0.154
3.37	Changed to 7.0					
	7.0	7	100	0.165	0.168	0.166
3.47	Changed to 7.8					
3.52	7.8	9	100	0.152	0.155	0.153

TABLE III

Expt. 35. Auricle

TIME	pH	NUMBER OF RECORD	DRIVEN RATE	SECONDS TO SIGNAL		CALCULATED REFRACTORY PERIOD
				Latest ineffective response	Earliest effective response	
3.21	Changed to 7.0					
3.30	7.0	4	94	0.209	0.219	0.214
3.31	Changed to 7.8					
3.35	7.8	5	94	0.199	0.203	0.201
3.39	7.8	6	94	0.192	0.193	0.192
3.40	Changed to 7.0					
3.50	7.0	8	94	0.209	0.215	0.212
3.51	Changed to 7.8					
4.00	7.8	10	94	0.182	0.184	0.183
4.01	Changed to 7.0					
4.17	7.0	15	91	0.202	0.216	0.209
4.18	Changed to 7.8					
4.28	7.8	17	91	0.186	0.187	0.186

results is apparent, the earliest effective response with a perfusate of pH 7.8 following 0.018 of a second earlier than that with a pH of 7.0.

The calculated refractory period determined as the average of the

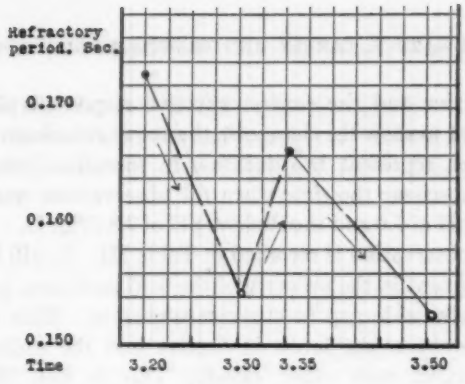

FIG. 1

Black dots represent acid perfusate of pH 7.0. Circles, an alkaline perfusate of pH 7.8. Ordinates represent duration of refractory period in seconds. Abscissae the time of the observation.

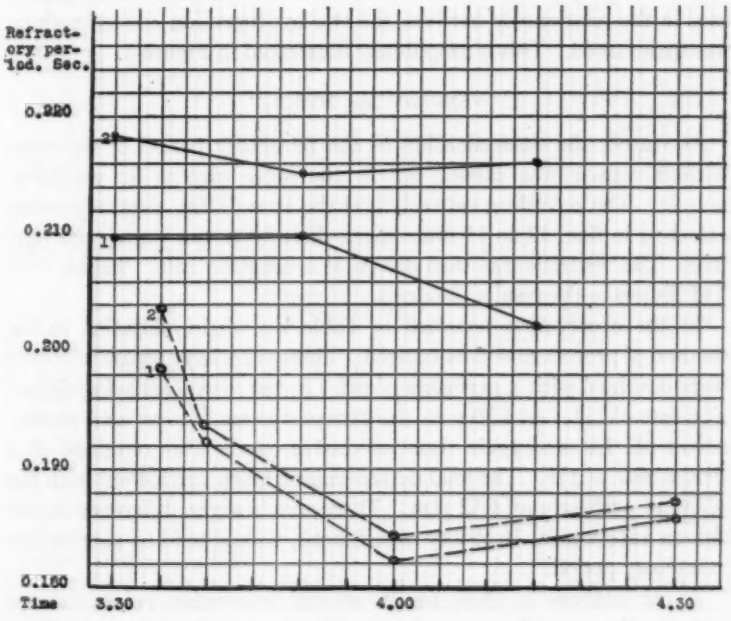

FIG. 2

Schema of graph as in Figure 1. Lines marked *1* represent latest ineffective response with acid and alkaline perfusate respectively. Lines marked *2*, the earliest effective response under similar conditions.

latest ineffective and the earliest effective response is plotted in the graph Figure 1 to show the changes in the above experiment (Table II). The ordinates represent the duration in seconds of the refractory period, the abscissae the time when the observations were made, the black dots a pH of 7.0 and the circles a pH of 7.8 (Fig. 1).

A similar observation is recorded in Table III. It will be seen that in this experiment in the presence of the acid perfusate, pH 7.0, there is an unusually wide gap in our measurements. With the alkaline perfusate, however, the latest ineffective and the earliest effective stimulus parallel each other closely. This is well illustrated in Figure 2.

A final observation upon auricular muscle is given in Table IV. These results are of interest in that, although there was a lengthening in the refractory period with the progress of the experiment, the difference in the relationship between the two hydrogen-ion concentrations was maintained. This is graphically illustrated in Figure 3.

VENTRICULAR MUSCLE

As stated, the determination of the refractory period of the ventricular muscle was carried out in the same way as for auricular muscle. The recording contacts and the stimulating electrodes were attached in line, 12 to 15 mm. apart, directly to the ventricular surface. The ventricle was then driven at a constant rate. Tables V to VII illustrate the results obtained.

In the observation recorded in Table V a slight variation in the method of procedure will be noticed. Three successive separate curves were obtained with a perfusate of pH 7.8, the ventricles being driven at a rate of 111. At 4.30 p.m. the change was made to an acid perfusate of pH 7.0, and again three successive curves were obtained at a driven rate of 115. The final determination being carried out with the alkaline perfusate at 4.52 p.m. There was a slight difference in the driven rate which, if of any significance, should tend to shorten the refractory period.

In an analysis of these results several interesting points are apparent: the general average increase in the length of the calculated refractory period over that determined for auricular muscle, the gradual increase in the time interval of the latest ineffective response seen

in successive records, and the fact that the figures for the final determination at 4.52 p.m., in the presence of the alkaline perfusate, agree so exactly with the earlier similar record taken at 4.29 p.m.,

TABLE IV

Expt. 36. Auricle

TIME	pH	NUMBER OF RECORD	DRIVEN RATE	SECONDS TO SIGNAL		CALCULATED REFRACTORY PERIOD
				Latest ineffective response	Earliest effective response	
3.27	Changed to 7.0					
3.37	7.0	3	115	0.171	0.178	0.174
3.39	Changed to 7.8					
3.50	7.8	5	115	0.161	0.168	0.164
3.52	Changed to 7.0					
4.03	7.0	7	115	0.190	0.198	0.194
4.05	Changed to 7.8					
4.15	7.8	9	115	0.182	0.190	0.186
4.17	Changed to 7.0					
4.21	7.0	10	115	0.214	0.215	0.215
4.25	Changed to 7.8					
4.36	7.8	13	115	0.192	0.194	0.193

TABLE V

Expt. 29. Ventricle

TIME	pH	NUMBER OF RECORD	DRIVEN RATE	SECONDS TO SIGNAL		CALCULATED REFRACTORY PERIOD
				Latest ineffective response	Earliest effective response	
4.18	Changed to 7.8					
4.23	7.8	5	111	0.194	0.201	0.197
4.28	7.8	6	111	0.204	0.208	0.206
4.29	7.8	7	111	0.214	0.222	0.218
4.30	Changed to 7.0					
4.34	7.0	8	115	0.222	0.226	0.224
4.39	7.0	9	115	0.226	0.236	0.231
4.43	7.0	10	115	0.239	0.241	0.240
4.45	Changed to 7.8					
4.52	7.8	11	115	0.214	0.221	0.217

though there was an interval of 23 minutes between these two records. It is significant that the determination of the refractory period

at 4.52 p.m. measures 0.023 less then the preceding determination with the perfusate of pH 7.0.

In the observation detailed above in Table VI the differences in the

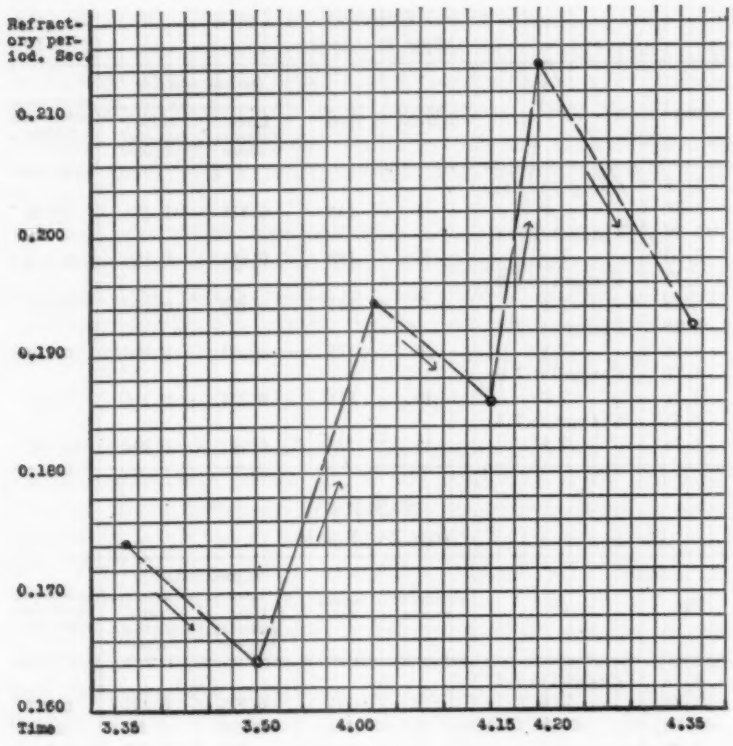

FIG. 3

Schema of graph the same. Illustrates contrast in duration of the refractory period with acid and alkaline perfusate and also increase in length of refractory period due to duration of experiment.

refractory period under the conditions of the experiment are apparent.

Although the experiment outlined in Table VII lasted an hour and twenty minutes there was apparently no appreciable alteration in the refractory period dependent upon the duration of the observation.

It is of interest that in this instance the refractory period determined in the presence of the normal pH falls approximately midway between the figures obtained upon the acid and alkaline side of neutrality.

TABLE VI

Expt. 30. Ventricle

TIME	pH	NUMBER OF RECORD	DRIVEN RATE	SECONDS TO SIGNAL		CALCULATED REFRACTORY PERIOD
				Latest ineffective response	Earliest effective response	
3.36	7.4	2	110	0.200	0.207	0.203
3.37	Changed to 7.0					
3.39	7.0	3	110	0.226	0.228	0.227
3.41	Changed to 7.8					
3.47	7.8	5	110	0.212	0.222	0.217
3.53	7.8	7	110	0.200	0.214	0.207
3.54	Changed to 7.0					
3.58	7.0	8	110	0.220	0.222	0.221
4.01	7.0	9	110	0.227	0.228	0.228

TABLE VII

Expt. 31. Ventricle

TIME	pH	NUMBER OF RECORD	DRIVEN RATE	SECONDS TO SIGNAL		CALCULATED REFRACTORY PERIOD
				Latest ineffective response	Earliest effective response	
3.53	7.4	3	110	0.218	0.219	0.219
3.55	Changed to 7.0					
3.58	7.0	4	110	0.220	0.228	0.224
4.28	7.0	9	110	0.228	0.237	0.232
4.39	Changed to 7.8					
4.48	7.8	12	110	0.196	0.201	0.198
4.56	Changed to 7.0					
5.05	7.0	15	110	0.220	0.228	0.224
5.07	Changed to 7.8					
5.15	7.8	17	110	0.193	0.195	0.194

In the experiment detailed above, Table VIII, the refractory period of the ventricular muscle approaches that encountered in the auricular muscle in our observations with a pH of 7.8. The single determination with the normal pH 7.4 falls between that obtained with

TABLE VIII

Expt. 32. Ventricle

TIME	pH	NUMBER OF RECORD	DRIVEN RATE	SECONDS TO SIGNAL		CALCULATED REFRACTORY PERIOD
				Latest ineffective response	Earliest effective response	
3.03	7.4	2	115	0.191	0.198	0.194
3.05	Changed to 7.0					
3.08	7.0	3	115	0.196	0.202	0.199
3.12	7.0	4	115	0.202	0.206	0.204
3.14	Changed to 7.8					
3.17	7.8	5	115	0.171	0.187	0.179
3.21	7.8	6	115	0.173	0.175	0.174
3.22	Changed to 7.8					
3.79	7.0	7	115	0.200	0.205	0.202
3.42	7.8	10	115	0.176	0.178	0.177

TABLE IX

Calculated determinations of the refractory period of the perfused hearts of dogs with a variation only in the hydrogen-ion concentration of the perfusate

AURICULAR MUSCLE			VENTRICULAR MUSCLE		
Driven rate	pH 7.0	pH 7.8	Driven rate	pH 7.0	pH 7.8
111	0.192	0.177	111		0.197
111		0.181	111		0.206
100	0.173	0.154	111		0.218
100	0.166	0.153	115	0.224	
94	0.214	0.201	115	0.231	
94		0.192	115	0.240	0.217
94	0.212	0.183	110	0.227	0.217
91	0.209	0.186	110	0.221	0.207
115	0.174	0.164	110	0.228	
115	0.194	0.186	110	0.224	0.198
115	0.215	0.193	110	0.232	
114	0.203	0.179	110	0.224	0.194
114		0.176	115	0.199	0.179
			115	0.204	0.174
			115	0.202	0.177
Average refractory period..	0.195	0.171		0.221	0.198

the perfusate of pH 7.0 and pH 7.8. The duration of the entire period of observation was approximately 40 minutes, and again there was no

apparent change in the response of the muscle dependent upon the length of the experiment. This table is graphically illustrated in Figure 4. Following the first two determinations with an acid perfusate at 3.08 p.m. and 3.12 p.m., the two determinations with an alkaline perfusate immediately afterwards, at 3.17 p.m. and 3.21 p.m., show a shortening of over 0.020 of a second. Ten minutes later with a pH of 7.0 the refractory period lengthens, to shorten again with the final determination at 3.42 p.m.

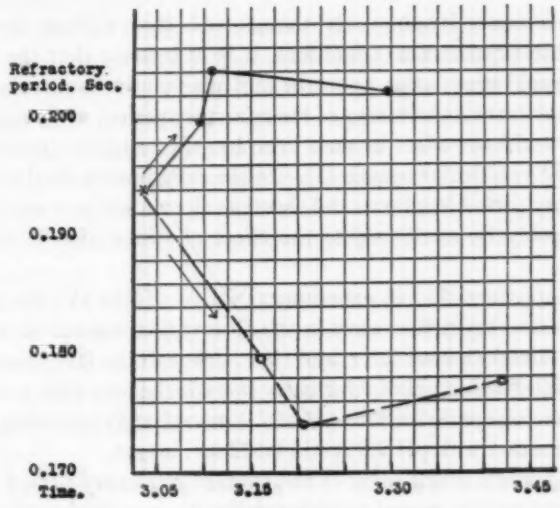

FIG. 4

Schema of graph as in other figures. x = determination of refractory period at beginning of experiment, with normal pH 7.4 and subsequent changes with an acid and alkaline perfusate.

If we tabulate our results in opposite columns the contrast is equally apparent.

DISCUSSION

In the perfused heart removed from the body one can exclude entirely the influence of the extrinsic cardiac nerves. This is of peculiar importance in connection with the possible influence of rapid stimu-

lation upon the vagus endings. Since, however, it is well known that in the perfused heart direct stimulation of the vagus is without effect soon after the perfusion is started (6), we may therefore interpret any changes obtained in the refractory period as arising independently of any effect of stimulation upon the vagus endings. As the changes noted occurred following an alteration in the pH alone of the perfusion fluid, all other conditions remaining constant, our interpretation of such variations in the duration of the refractory period seems justifiable.

In this connection, however, though we believe without significance under the experimental conditions, it is of interest that the effect of direct vagal stimulation upon the auricular muscle is associated with slight but definite shortening of the refractory period, while such stimulation is without effect or may even lengthen slightly the refractory period of ventricular muscle (5). In the experiments cited above, the refractory period lengthens and shortens alternately in a way that can not possibly be attributed to the effect of stimulation of the vagal endings.

It is apparent that in experiment No. 36 (Table IV) the duration of the refractory period early in the observation is much shorter than that obtained an hour later, and that, although the last measurement determined with a pH of 7.8 greatly exceeds the first with a pH of 7.0, the refractory period with a pH of 7.0 immediately preceding the last determination with pH 7.8 is still 0.022 sec. longer.

This gradual lengthening of the average refractory period we have attributed to the general nutritional disturbances taking place in the cardiac muscle. With the shorter observations this gradual prolongation was not apparent (see Expt. 32, Table VIII). Whatever the nature of the changes occurring in the muscle may be under the artificial conditions of the experiment, leading to this gradual increase in the length of the refractory period, it is significant that the qualitative differences with the change in the hydrogen-ion concentration persist.

In constructing the graphic figures illustrating the changes encountered, three types have been made use of. In Figures 1 and 3 the calculated sequential average refractory periods have been plotted. In Figure 4, the measurement obtained with a normal pH 7.4 has been charted and the succeeding determinations with the acid and the

alkaline perfusate have been plotted and united by straight lines. In Figure 2 the latest ineffective and the earliest effective break shocks are plotted and connected.

It is at once evident that in the observation represented by this figure (Exp. 35, Table III) there is a fairly wide gap in the measurements obtained with the acid perfusate, while the determinations with the alkaline perfusate parallel each other quite closely. This gap in the determinations with the acid perfusate illustrates well the lability of the refractory period and of the experimental precedure. The conditions of this particular observation, in so far as could be judged, were ideal in every way. There was no gradual lengthening of the refractory period due to the length of the experiment, the technical procedure was the same throughout, and the actual measurements alone revealed the striking contrast between the two curves. It is of interest that the interval between the earliest effective stimuli lengthens with the progress of the experiment, the duration of the refractory period with the alkaline perfusate actually shortening below the first determination at 3.40.

In the light of what is known from the work of Mines (6, 7), Dale and Thacker (2), Drury and Andrus (4), and our studies, referred to above (1), upon the reaction of the cardiac tissue to changes in the hydrogen-ion concentration, it seemed highly probable that the refractory period might show demonstrable alterations to changes in the pH of the perfusion fluid.

It is, however, of significance that the changes actually encountered occur so abruptly and are in some instances at least so great, the actual difference varying from 0.008 to 0.033 sec. The abruptness and decisiveness of the changes noted is, it seems to us, more fundamentally important than any magnitude of difference, although reference to Table IX it will show that on the basis of the average of 23 observations upon auricular muscle the difference in the refractory period between a pH of 7.0 and one of 7.8 is found to be 0.024 sec., while for a similar series of observations upon ventricular muscle it is 0.023 sec.

SUMMARY

It is apparent that with a change only in the hydrogen-ion concentration of the perfusion fluid throughout so narrow a range as pH 7.0 to pH 7.8, there follows an abrupt and significant alteration in the refractory period of both auricular and ventricular muscle of the perfused dog's heart, the refractory period being lengthened with the acid and shortened with the alkaline perfusate.

The importance of this alteration in the duration of the refractory period in relation to re-entrant waves, circus movements and changes in the transmission interval in cardiac muscle suggests itself and is to be emphasized.

It is conceivable that in the myocardium, the seat of local disease processes in man, such regional changes in the hydrogen-ion concentration may occur as to modify the refractory period of the tissue involved, leading to disturbances in the normal sequence of events as suggested above.

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2. Dale and Thacker: *Jour. of Physiol.*, 1914, xlvii, 493.
3. Dieuaide and Turner: *Johns Hopkins Hosp. Bull.*, 1924, xxxv, 411.
4. Drury and Andrus: *Heart*, 1924, xi, 389.
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9. *Idem:* Jour. of Physiol., 1913, xlvi, 349–383.

FOREIGN BODY CYSTS SIMULATING PARASITIC CYSTS OF THE PERITONEAL CAVITY[1]

C. G. GUTHRIE, M.D.
Lawrenceville, New Jersey

The case to be reported is, I believe, unique and so perhaps of some interest, but as it is at most a medical curiosity rather than of any real importance, the utmost brevity is warranted in its presentation.

The patient was an unmarried man of 31, a Syrian, employed as a machinist in the coal regions of West Virginia, who visited the hospital to consult Dr. R. H. Follis regarding "a pain in the stomach."

He came to this country at 17. Tapeworm segments were noticed in his stools from the time he was 23 until the worm was expelled "head and all" about two years later (at 25); beyond the fact that it was a long worm, he could give no details that would assist in identification of the parasite.

For four years (27 to 31) he had suffered from "digestive trouble" occurring at intervals, manifested by pain in the epigastrium and discomfort sometime after eating but not accompanied by nausea or vomiting. At 28, following prolonged physical exertion, he had a very severe attack of pain in the right hypochrondrium, so severe that he fell to the ground, could breathe only with the greatest difficulty, and found it necessary to lie on his right side. Nausea and vomiting were persistent, but he was too ill to feel any interest in the character of the vomitus. He was prostrated for six days and unable to return to work for a month. There was a gradual revovery from the acute attack, but since then, in addition to the epigastric discomfort after eating, there have been attacks of pain in the gall-bladder region associated with moderate jaundice lasting for two or three days.

Nine months ago (age 30) he was submitted to an exploratory laparotomy in a hospital in West Virginia at which time a diagnosis of cysticercus disease was made and the incision closed. Three weeks

[1]Read before the Association of American Physicians, Atlantic City, New Jersey, May 3–5, 1926. Received for publication June 29, 1926.

were devoted to convalescence in the hospital and four more after he was discharged, but he experienced no relief of symptoms. Two severe attacks of pain with jaundice and several milder ones occurred in the subsequent nine months. Shortly after the operation he developed a new symptom—the ingestion of fluids, even a glass of water, was followed immediately by a sharp pain in the epigastrium.

On admission to the hospital, the physical findings were essentially negative except for slight jaundice, the presence of two operative scars, one in the epigastrium, the other in the right hypochondrium, and moderate tenderness on palpation in the right upper portion of the abdomen. The liver and spleen were not enlarged; no free fluid could be demonstrated; no masses, muscle spasm or abnormal peristaltic waves were made out. The pulse, temperature, respiration, and blood pressure were normal.

Gastric analysis showed some retention and a moderately high free and total acidity. Repeated examinations of the stools revealed no parasites, parasitic ova, or other abnormality. The Wassermann test and examination of the blood and urine were negative. The x-ray report showed that there was a dilated stomach with the pylorus pulled to the right; retention but no actual obstruction; a persistent filling defect in the pyloric region; the findings suggesting either an ulcerative lesion at the pylorus or, more probably, adhesions in the right upper quadrant.

From the practical, surgical standpoint the patient had abdominal adhesions causing symptoms which might be relieved if the adhesions were released. His story, however, suggested very interesting possibilities: a foreigner; infestation by a tapeworm, possibly *Taenia solium* which is capable of causing cysticercus disease in man; following expulsion of the worm, digestive difficulties and abdominal pain for years; an exploratory operation with a diagnosis of cysticercus disease; this was more than enough to ensure my presence at the operation.

FIG. 1

Above: encysted seeds in wall of small intestine. *a* and *b:* cysts in omentum opened showing seeds in interior. *c*, *d* and *e:* exterior and sagittal section of raspberry seeds from cysts. *f* and *g:* exterior and sagittal section of tomato seeds from cysts.

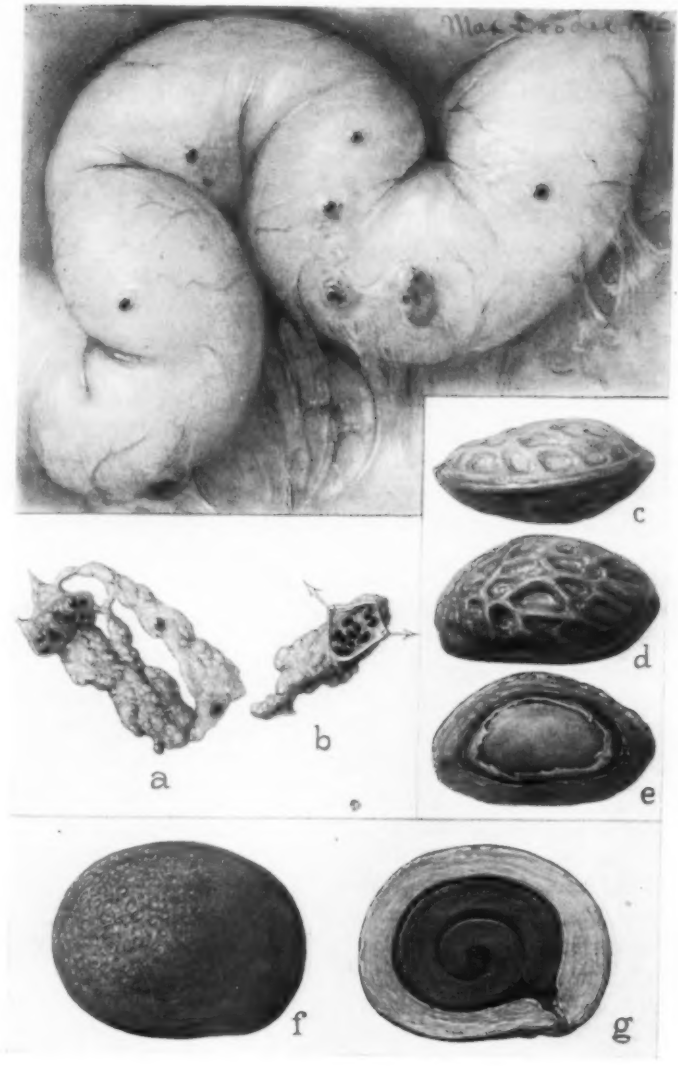

FIG. 1

Dr. Follis made a high right rectus incision and found dense adhesions everywhere between the parietal peritoneum, the omentum and the stomach; these it was necessary to free before the peritoneal cavity proper could be exposed. It was then found that the stomach wall was pulled up and adherent at the site of the epigastric incision made at the previous operation. Numerous, dense adhesions were present about the pylorus, the gall-bladder, the edge of the liver and extending down the right side almost to the brim of the pelvis, rendering exposure very difficult. When a view of the peritoneal cavity was obtained, numerous small round or oval cystic bodies were seen everywhere over the surface of the intestine, in the mesentery, the omentum, the adhesions, and attached to the gall-bladder. They were particularly abundant on the right side and could be felt studded over the parietal peritoneum as far down as the caecum. These cysts varied from 5 to 15 mm. in diameter, the majority being well within these extremes. In shape they were, for the most part, spherical but others were flattened and bean-shaped. They were smooth and glistening, opaque and white, but many of them showed the presence of something dark in the interior. Several of those in the omentum were excised and given to me for examination which promptly showed that these bodies were certainly not cysticerci and probably not of parasitic origin at all. The adhesions, accordingly, were freed, the wound closed and the patient returned to the ward.

The cysts were composed of a tough membrane or envelope containing from one to eight or nine dark, hard bodies, quite resistant to crushing, from 1.5 to 3 mm. in diameter, some round and flattened or disc-shaped, others more elongate. When seen under the microscope, they were easily recognized as vegetable seeds and were later identified as raspberry and tomato seeds.

The probable course of events could then be reconstructed with considerable assurance. The patient evidently had had a gastric or duodenal ulcer. At the time of his severe pain and collapse, the ulcer had perforated and the gastric contents (merely the residue, in all likelihood) had entered the peritoneal cavity. The foreign bodies so introduced were surrounded by fibrin, eventually covered by peritoneum and rendered innocuous. The adhesive peritonitis resulting from the perforation was responsible for the symptoms that fol-

lowed. The relatively recent epigastric pain immediately after swallowing a glass of water could be attributed to the pull thus produced on the stomach adherent to the operative scar. The patient made an uneventful recovery and left the hospital freed from the symptoms from which he sought relief.

From the patient the information was later elicited that the last meal he had eaten prior to the perforation had consisted largely of cooked canned tomatoes and bread spread with raspberry jam. This offered an excellent reason for our failure to secure germination of the seeds recovered after several years' residence in the abdominal cavity. Recalling Baron Munchausen's adventure with the stag and the cherry stones, however, it was but natural to speculate as to what might have been their fate had the seeds been viable when introduced into the peritoneal cavity of our patient. With tomato seeds fresh from the market, germination was secured in a few days (3 or 4) by planting them on moist cotton in the laboratory. With raspberry seeds it was not so simple, as the shells are resistant and require filing or other artificial aid to replace that provided in nature by freezing or the trituration with sand and stones in the crops and gizzards of birds. Having determined that about 90 per cent of the tomato seeds from our particular lot could be counted upon to germinate promptly on moist cotton and that this was unhindered by previous immersion of the seeds in 0.85 per cent saline solution or in hydrochloric acid of such concentration as might be found in the gastric juice, we tested their ability to grow in the peritoneal cavity of rabbits. The animals seemed to thrive; when they were sacrificed three to four weeks later, there was no excess of peritoneal fluid and cultures from the cavity gave no growth on ordinary media. The seeds were found in groups of five or six to a dozen or more, completely enmeshed in a tough, thick layer of fibrin located for the most part between coils of the small intestine; none of them had germinated. Botanists point out that seeds would probably fail to germinate in this location, even though they were not surrounded by a fibrin envelope, owing to the lack of available oxygen.

BOOK REVIEWS

Baltimore, July 3, 1926.

TO THE EDITOR:

I would like to acknowledge through the BULLETIN the receipt, from our Medical School Alumni, of $3710.50, which has been handed in a check to Miss Minnie W. Blogg, our Librarian, as an expression of the warm personal interest felt by many of our graduates and their appreciation of her services in the Hospital Library. Doctor Barker and Doctor Young, being unavoidably absent, Doctors Henry Barton Jacobs and Grant E. Ward and I formed a little committee to convey the gift to Miss Blogg whom we found at her accustomed place in the Library.

With this acknowledgment, I desire to discharge myself from the very pleasant function of a collector of the Fund, and to express to the various donors my hearty appreciation of their prompt, generous and effective coöperation.

HOWARD A. KELLY.

Review of the Diagnosis, Treatment and End Results of Tuberculous Disease of the Hip Joint. By GEORGE PERKINS. 118 pp. $1.75. (*Oxford Medical Publications, Humphrey Milford, London, 1926.*)

This monograph on tuberculosis of the hip has been excellently worked up and is well worth reading. It is most worthy of the award of the Robert Jones Prize. It is a thorough inquiry into the treatment and end results of 50 cases. No attempt has been made to cover the subject from every aspect.

Emphasis is laid on the early diagnosis of the condition. There are very clear radiographic pictures of the different types of disease, such as that involving the acetabulum, the head and the neck of the femur, which deserve especial attention and study. The head was affected in 80 per cent of the cases studied. Emphasis is laid on the non-operative treatment (recumbency, traction and fixation), and the general treatment (open air, hygiene and heliotherapy). The only operative treatment recommended is an arthrodesis of the joint in selected cases. In the final results studied all of the patients have been under the care of the surgeon for years. Stress is laid on the fact that once a doctor has undertaken to treat a case of tuberculosis of the hip, the patient should be followed for a lifetime.

A detailed description of the Pyrford Frame used in the treatment of this disease is given. This is a combination of the Bradford Spinal Frame and the Jones Abduction Hip Splint. A special carriage for the transportation of the patient to the outside is shown, called the Carshalton Carriage. Mention is made of Diaplyte—the Dreyer Vaccine for tuberculosis, but it is thought to be of no value in treating tuberculosis of the joints.

A. R. S., JR.

Modern Methods of Feeding in Infancy and Childhood. By DONALD PATERSON and J. FOREST SMITH. 106 pp. $3.00. (*Paul B. Hoeber, New York, 1926.*)

The importance of breast feeding is rightly emphasized and the use of many proprietary foods for infant feeding is explained. The tables of analyses of various types of milk and patent foods and the descriptions of their composition will be helpful to those who prescribe these diets.

A. E. F.

Methods in Surgery. By GLOVER H. COPHER, M.D. 232 pp. $3.00. (*The C. V. Mosby Company, St. Louis, 1925.*)

This book which covers the various routine and special procedures employed on the Surgical Service at the Barnes and the St. Louis Children's Hospital will be of value to those especially interested in hospital methods. Locally it should serve a very useful purpose, but it is of little general interest.

W. A. N.

Nephritis. By HERMAN ELWYN, M.D. pp. 347. $5.00. (*The Macmillan Company, New York, 1926.*)

The author presents the various forms of nephritis, endeavoring to correlate the clinical findings with the pathological changes, and following to a great extent the classification of Volhard.

The book begins with a discussion of the normal function of the kidney and, although the treatment of the experimental work is somewhat brief, one obtains a fairly clear conception of the evidence to date regarding these problems. Renal insufficiency, hypertension and uremia are considered before the author attempts to classify the individual forms of nephritis, which he groups into glomerulo-nephritis, nephrosis or tubular degenerative nephritis, and the arterio-sclerotic diseases of the kidney. Each of these three groups is further subdivided; the glomerulo-nephritis group includes the focal (embolic and non-embolic) and the diffuse (acute, subacute, subchronic and chronic) types; the nephrosis group the pregnancy, lipoid, amyloid and bichloride kidneys; and the arterio-sclerotic group the forms affecting the renal artery, its branches and the smaller vessels or arterioles. Each group is discussed in detail with some suggestions as to treatment. In certain instances, the author makes rather binding statements on questions still under dispute, *e.g.*, he explains eclampsia wholly on the basis of kidney trouble. In a treatise like the one under discussion, one would rather see an unbiased presentation of the subject matter with as much experimental data as seems appropriate. The book is, however, a very clear and concise presentation of nephritis, tempered to a large extent by the author's own views.

H. J. S.

Pernicious Anemia. By FRANK A. EVANS. 178 pp. $2.70. (*The Williams & Wilkins Co., Baltimore, Md., 1926.*)

To write a book on pernicious anaemia is a difficult undertaking. Evans has,

within the limits set himself, produced a good, succinct description of the disease. The omission of historical data, while making the book smaller, robs it of much value, since the disease "as understood at present," can best be appreciated by tracing the development of our knowledge. No fault can be found with the classification of anaemias presented. He wisely emphasizes the inclusive nature of the disease, demanding more than anaemia for our conception of it. He is to be congratulated for at least one very needful remark: "If, in the presence of a severe anaemia, anisocytosis is not frankly present, the condition is surely not pernicious anaemia." The section on etiology is a trifle fragmentary and does not really present a good critical review of work done. Evans' doubt about the occurrence of peripheral nerve degeneration might be readily dissipated by reading Hamilton and Nixon's most conclusive report on this subject. The chapter on treatment is judicial, although perhaps justice is scarcely done to Fowler's solution. Evans believes that abnormal lipoid metabolism plays some etiological rôle. After all, one's opinion of the cause of pernicious anaemia is a matter of personal conviction and, as in the case of religion and politics, corrective data are hard to obtain.

B. S. C.

Nursery Guide for Mothers and Children's Nurses. By LOUIS W. SAUER, PH.D., M.D. Pp. 206. $2.00. (*The C. V. Mosby Company, St. Louis.*)

Dr. Sauer's book has become so favorably known that there is little need for comment other than to record the issuance of a new edition. The general care of the infant, a study of nutritional disturbances and careful feeding directions are all discussed in detail. Advice and diets for older children have been added. One regrets that his warnings against artificial feeding, condensed milk, and excessive medication are not sufficiently emphasized and repeated, but have become partially lost in the mass of facts. This, however, is the type of book which not only aids the mother and doctor but should prove a most effective agent in the reduction of infant mortality.

P. E. R.